

PATENT COOPERATION TREATY

PCT

NOTIFICATION CONCERNING
DOCUMENT TRANSMITTED

From the INTERNATIONAL BUREAU

To:

United States Patent and Trademark
Office
Washington, D.C.

Date of mailing:

14 June 1993 (14.06.93)

in its capacity as elected Office

International application No.:

PCT/GB92/01082

International filing date:

17 June 1992 (17.06.92)

Applicant:

SMITHKLINE BEECHAM PLC et al

The International Bureau transmits herewith the following documents and number thereof:

copy of the international preliminary examination report and annexes (Article 36(3)(a))

The International Bureau of WIPO
34, chemin des Colombettes
1211 Geneva 20, Switzerland

Facsimile No.: (41-22) 740.14.35

Authorised officer:

M. Abidine

Telephone No.: (41-22) 730.91.11

PATENT COOPERATION TREATY

PCT

From the INTERNATIONAL BUREAU

NOTIFICATION OF ELECTION

(PCT Rule 61.2)

United States Patent and Trademark
Office
Washington, D.C.

Date of mailing: 07 January 1993 (07.01.93)	in its capacity as elected Office
International application No.: PCT/GB92/01082	Applicant's or agent's file reference: JF/JMcD/P30104
International filing date: 17 June 1992 (17.06.92)	Priority date: 26 June 1991 (26.06.91)
Applicant: SMITHKLINE BEECHAM PLC et al	

1. The designated Office is hereby notified of its election made:

in the demand filed with the International preliminary Examining Authority on:

30 November 1992 (30.11.92)

in a notice effecting later election filed with the International Bureau on:

2. The election was

was not

made before the expiration of 19 months from the priority date

<p>The International Bureau of WIPO 34, chemin des Colombettes 1211 Geneva 20, Switzerland</p> <p>Facsimile No.: (41-22) 740.14.35</p>	<p>Authorized officer:</p> <p>J. Zahra</p> <p>Telephone No.: (41-22) 730.91.11</p>
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PATENT COOPERATION TREATY
PCT

27

INTERNATIONAL PRELIMINARY EXAMINATION REPORT 11 JULY 1993

(PCT Article 36 and Rule 70)

WIPO PCT

Applicant's or agent's file reference JF/JMcD/P30104	For Further Action	See Notification of Transmittal of International Preliminary Examination Report (Form PCT/IPEA/416)
International Application No. PCT/GB_92/01082	International Filing Date (day/month/year) 17 JUNE 1992	Priority Date (day/month/year) 26 JUNE 1991
International Patent Classification (IPC) A61K 31/40, C07D 209/88		
Applicant SMITHKLINE BEECHAM PLC ET AL		

<p>1. This international preliminary examination report has been prepared by this International Preliminary Examining Authority and is transmitted to the applicant according to Article 36.</p> <p>2. This REPORT consists of a total of 5 sheets.</p> <p><input checked="" type="checkbox"/> This report is also accompanied by ANNEXES i.e., sheets of the description, claims and/or drawings amended during international preliminary examination and/or containing rectifications made before this Authority.</p> <p>These annexes consist of a total of 4 sheets.</p>																										
<p>3. This report contains indications relating to the following items:</p> <table style="width: 100%; border-collapse: collapse;"> <tr> <td style="width: 10%; text-align: right; padding-right: 10px;">I</td> <td style="width: 10%; text-align: center; padding-right: 10px;"><input checked="" type="checkbox"/></td> <td style="width: 80%; padding-right: 10px;">Basis of the report</td> </tr> <tr> <td style="text-align: right; padding-right: 10px;">II</td> <td style="text-align: center; padding-right: 10px;"><input type="checkbox"/></td> <td style="padding-right: 10px;">Priority</td> </tr> <tr> <td style="text-align: right; padding-right: 10px;">III</td> <td style="text-align: center; padding-right: 10px;"><input checked="" type="checkbox"/></td> <td style="padding-right: 10px;">Non-establishment of opinion with regard to novelty, inventive step and industrial applicability</td> </tr> <tr> <td style="text-align: right; padding-right: 10px;">IV</td> <td style="text-align: center; padding-right: 10px;"><input type="checkbox"/></td> <td style="padding-right: 10px;">Lack of unity of invention</td> </tr> <tr> <td style="text-align: right; padding-right: 10px;">V</td> <td style="text-align: center; padding-right: 10px;"><input checked="" type="checkbox"/></td> <td style="padding-right: 10px;">Reasoned statement with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement</td> </tr> <tr> <td style="text-align: right; padding-right: 10px;">VI</td> <td style="text-align: center; padding-right: 10px;"><input type="checkbox"/></td> <td style="padding-right: 10px;">Certain documents cited</td> </tr> <tr> <td style="text-align: right; padding-right: 10px;">VII</td> <td style="text-align: center; padding-right: 10px;"><input type="checkbox"/></td> <td style="padding-right: 10px;">Certain defects in the international application</td> </tr> <tr> <td style="text-align: right; padding-right: 10px;">VIII</td> <td style="text-align: center; padding-right: 10px;"><input checked="" type="checkbox"/></td> <td style="padding-right: 10px;">Certain observations on the international application</td> </tr> </table>			I	<input checked="" type="checkbox"/>	Basis of the report	II	<input type="checkbox"/>	Priority	III	<input checked="" type="checkbox"/>	Non-establishment of opinion with regard to novelty, inventive step and industrial applicability	IV	<input type="checkbox"/>	Lack of unity of invention	V	<input checked="" type="checkbox"/>	Reasoned statement with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement	VI	<input type="checkbox"/>	Certain documents cited	VII	<input type="checkbox"/>	Certain defects in the international application	VIII	<input checked="" type="checkbox"/>	Certain observations on the international application
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VI	<input type="checkbox"/>	Certain documents cited																								
VII	<input type="checkbox"/>	Certain defects in the international application																								
VIII	<input checked="" type="checkbox"/>	Certain observations on the international application																								

Date of submission of the demand 30 NOVEMBER 1992	Date of completion of this report 7 JUNE 1993
Name and mailing address of the IPEA The Patent Office Cardiff Road NEWPORT Gwent NP9 1RH	Authorized Officer S J QUICK
Facsimile No 0633 814444	Telephone No 0633 813534

I. Basis of the report

1. This report has been drawn on the basis of:

the international application as originally filed.

the description, pages 1-4 and 6-37, as originally filed,
pages, filed with the demand,
page 5, filed with the letter of 26 April 1993
pages, filed with the letter of

the claims, pages 38, 41 and 42, as originally filed,
pages, as amended under Article 19,
pages, filed with the demand,
pages 39, 40 and 43, filed with the letter of 26 April 1993
pages, filed with the letter of

the drawings, sheets, as originally filed,
sheets, filed with the demand,
sheets, filed with the letter of
sheets, filed with the letter of

2. The amendments have resulted in the cancellation of: pages:

sheets of drawings No: —

3. This report has been established as if (some of) the amendments had not been made, since they have been considered to go beyond the disclosure as filed, as indicated in the Supplemental Box.

4. Additional observations, if necessary:

II. Priority

1. This report has been established as if no priority had been claimed due to the failure to furnish within the prescribed time limit the requested:

copy of the earlier application whose priority has been claimed.

translation of the earlier application whose priority has been claimed.

2. This report has been established as if no priority had been claimed due to the fact that the priority claim has been found invalid.

Thus for the purposes of this report, the international filing date indicated above is considered to be the relevant date.

III. Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

The questions whether the claimed invention appears to be novel, to involve an inventive step (to be non-obvious), or to be industrially applicable have not been and will not be examined in respect of:

the entire international application.

claim No 8

because:

the said international application, or the said claim No 8 relate to the following subject matter which does not require an international preliminary examination (*specify*):

Methods for treatment of the human or animal body by surgery or therapy, as well as diagnostic methods; Rule 67.1(iv).

the description, claims or drawings (indicate particular elements below) or said claims Nos . are so unclear that no meaningful opinion could be formed (*specify*):

the claims or said claims Nos . are so inadequately supported by the description that no meaningful opinion could be formed.

no international search report has been established for said claims Nos .

V. Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. STATEMENT

Novelty (N)	claims 1-7 and 9-10 claims	YES NO
Inventive Step (IS)	claims 1-7 and 9-10 claims	YES NO
Industrial Applicability (IA)	claims 1-7 and 9-10 claims	YES NO

2. CITATIONS AND EXPLANATIONS

Claims 1-7 and 9-10 meet the requirements of novelty and inventive step since none of the documents listed in the International Search Report disclose or suggest the subject matter of the amended claims of this application.

VIII. Certain observations on the international application

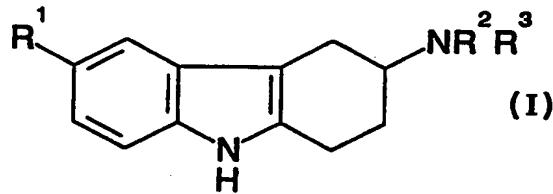
The following observations on the clarity of the claims, description, and drawings or on the question whether the claims are fully supported by the description, are made:

The text at page 3, lines 20-24, and at page 6, line 34 to page 7, line 2 is inappropriate in view of Rule 67.1(iv) and the invention as claimed.

INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(51) International Patent Classification 5 : A61K 31/40, C07D 209/88		A1	(11) International Publication Number: WO 93/00086
(21) International Application Number: PCT/GB92/01082		(43) International Publication Date: 7 January 1993 (07.01.93)	
(22) International Filing Date: 17 June 1992 (17.06.92)		(74) Agents: FLORENCE, Julia, A. et al.; Corporate Patents, SmithKline Beecham, Mundells, Welwyn Garden City, Hertfordshire AL7 1EY (GB).	
(30) Priority data: 9113802.4 26 June 1991 (26.06.91) GB		(81) Designated States: AT, AU, BB, BG, BR, CA, CH, CS, DE, DK, ES, FI, GB, HU, JP, KP, KR, LK, LU, MG, MW, NL, NO, PL, RO, RU, SD, SE, US, European patent (AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LU, MC, NL, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, SN, TD, TG).	
(71) Applicant (for all designated States except US): SMITH-KLINE BEECHAM PLC [GB/GB]; New Horizons Court, Brentford, Middlesex TW8 9EP (GB).		(72) Inventors; and (75) Inventors/Applicants (for US only) : KING, Francis, David [GB/GB]; GASTER, Laramie, Mary [GB/GB]; Smith-Kline Beecham Pharmaceuticals, Coldharbour Road, The Pinnacles, Harlow, Essex CM19 5AD (GB). KAU-MANN, Alberto, Julio [AR/GB]; YOUNG, Rodney, Christopher [GB/GB]; SmithKline Beecham Pharmaceuticals, The Frythe, Welwyn, Hertfordshire AL6 9AR (GB).	Published With international search report.

(54) Title: USE OF TETRAHYDROCARBAZONE DERIVATIVES AS 5HT₁ RECEPTOR AGONISTS



(57) Abstract

Use of a compound of general formula (I), wherein R¹ represents hydrogen, halogen, trifluoromethyl, nitro, hydroxy, C₁₋₆alkyl, C₁₋₆alkoxy, arylC₁₋₆alkoxy, -CO₂R⁴, -(CH₂)_nCN, -(CH₂)_nCONR⁵R⁶, -(CH₂)_nSO₂NR⁵R⁶, C₁₋₆alkanoylamino(CH₂)_n, or C₁₋₆alkylsulphonylamino(CH₂)_n; R⁴ represents hydrogen, C₁₋₆alkyl or arylC₁₋₆alkyl; R⁵ and R⁶ each independently represent hydrogen or C₁₋₆alkyl, or R⁵ and R⁶ together with the nitrogen atom to which they are attached form a ring; n represents 0, 1 or 2; and R² and R³ each independently represent hydrogen, C₁₋₆alkyl or benzyl or together with the nitrogen atom to which they are attached form a pyrrolidino, piperidino or hexahydroazepino ring; or a physiologically acceptable salt thereof, in the manufacture of a medicament for the treatment of a condition where a 5-HT₁-like agonist is indicated, for example migraine. Novel compounds of formula (I), processes for preparing them and pharmaceutical compositions containing them are also described.

INTERNATIONAL SEARCH REPORT

International Application

PCT/GB 92/01082

I. CLASSIFICATION OF SUBJECT MATTER (If several classification symbols apply, indicate all)⁶

According to International Patent Classification (IPC) or to both National Classification and IPC
Int.C1.5 A 61 K 31/40 C 07 D 209/88

II. FIELDS SEARCHED

Minimum Documentation Searched⁷

Classification System	Classification Symbols	
Int.C1.5	A 61 K	C 07 D

Documentation Searched other than Minimum Documentation
to the Extent that such Documents are Included in the Fields Searched⁸

III. DOCUMENTS CONSIDERED TO BE RELEVANT⁹

Category °	Citation of Document, ¹¹ with indication, where appropriate, of the relevant passages ¹²	Relevant to Claim No. ¹³
X	<p>Journal of Neurochemistry, vol. 35, no. 3, 1981, E. FRIEDMAN et al.: "Effects of conformationally restrained analogues of serotonin on its uptake and binding in rat brain", pages 931-937, see abstract; page 932, table 1</p> <p>---</p>	6,7,10
A	<p>---</p> <p>4?</p>	1-5,8,9
X	<p>Journal of Neurochemistry, vol. 28, no. 5, 1977, E. MELLER et al.: "Tetrahydro-beta-carbolines: specific inhibitors of type A monoamine oxidase in rat brain", pages 995-1000, see table 1, page 996; page 997, column 2, paragraph 2, table 2; page 998, table 3</p> <p>---</p>	6,7,10

° Special categories of cited documents : ¹⁰

"A" document defining the general state of the art which is not considered to be of particular relevance

E earlier document but published on or after the international filing date

1 document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

•^o document referring to an oral disclosure, use, exhibition or other means

•P document published prior to the int later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step

Y document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

IV. CERTIFICATION

Date of the Actual Completion of the International Search 13-08-1992	Date of Mailing of this International Search Report 20.10.92
International Searching Authority EUROPEAN PATENT OFFICE	Signature of Authorized Officer 

III. DOCUMENTS CONSIDERED TO BE RELEVANT (CONTINUED FROM THE SECOND SHEET)

Category ^o	Citation of Document, with indication, where appropriate, of the relevant passages	Relevant to Claim No.
A	---	1-5,8,9
X	EP,A,0004342 (E.I. DU PONT DE NEMOURS & CO.) 3 October 1979, see page 3, lines 1-28; pages 6-13 ---	6,7,10, 9
X	NL,A,7211102 (STERLING DRUG INC.) 14 August 1972, see page 1, line 1 - page 2, line 12; formulasheet, reactionscheme ---	9,10
X	Journal of Chemical Society, no. 2, 1970, G.E.A. COOMBES et al.: "Synthesis of 3-amino-1,2,3,4-tetrahydro-6-hydroxycarbazole, analogue of 5-hydroxytryptamine", pages 325-326, see whole document ---	6,9
A	Recenti Progressi in Medicina, vol. 80, no. 12, December 1989, J.W. LANCE: "Headache: classification, mechanism and principles of therapy, with particular reference to migraine", pages 673-680, see whole document ---	1-5,8
A	EP,A,0115607 (MERCK) 15 August 1984, see abstract; page 24, lines 11-26 -----	1-5,8

ANNEX TO THE INTERNATIONAL SEARCH REPORT
ON INTERNATIONAL PATENT APPLICATION NO.

GB 9201082
SA 60614

This annex lists the patent family members relating to the patent documents cited in the above-mentioned international search report. The members are as contained in the European Patent Office EDP file on 15/10/92. The European Patent Office is in no way liable for these particulars which are merely given for the purpose of information.

Patent document cited in search report	Publication date	Patent family member(s)		Publication date
EP-A- 0004342	03-10-79	US-A- 4254134		03-03-81
		AU-B- 524626		23-09-82
		AU-A- 4515079		20-09-79
		CA-A- 1107287		18-08-81
		JP-A- 54130563		09-10-79
		SU-A- 900807		23-01-82
		US-A- 4343812		10-08-82
<hr/>				
NL-A- 7211102	20-02-73	AT-B- 317200		12-08-74
		AT-B- 323733		25-07-75
		AT-B- 323734		25-07-75
		AU-B- 475251		19-08-76
		AU-A- 4559772		21-02-74
		BE-A- 787537		14-02-73
		CA-A- 965794		08-04-75
		CH-A- 554333		30-09-74
		CH-A- 554334		30-09-74
		CH-A- 554332		30-09-74
		DE-A- 2240211		22-02-73
		FR-A, B 2150781		13-04-73
		GB-A- 1373311		06-11-74
		SE-B- 386438		09-08-76
		US-A- 3959309		25-05-76
		US-A- 4224335		23-09-80
		US-A- 4172834		30-10-79
<hr/>				
EP-A- 0115607	15-08-84	DE-A- 3300094		05-07-84
		DE-A- 3336643		25-04-85
		AU-B- 566688		29-10-87
		AU-A- 2286483		05-07-84
		CA-A- 1259618		19-09-89
		US-A- 4547576		15-10-85
		US-A- 4618614		21-10-86
		US-A- 4698351		06-10-87
		JP-A- 60081181		09-05-85
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PATENT COOPERATION TREATY

Rapid

From the INTERNATIONAL SEARCHING AUTHORITY

PCT

**NOTIFICATION OF TRANSMITTAL OF
THE INTERNATIONAL SEARCH REPORT
OR THE DECLARATION**

(PCT Rule 44.1)

To:
SMITHKLINE BEECHAM
 Corporate Patents
 Attn. Mrs. J.A. Florence
 Mundells
 WELWYN GARDEN CITY, HERTS AL7 1EY
 UNITED KINGDOM

Date of mailing
 (day/month/year)

20.10.92

Applicant's or agent's file reference
JF/JMcD/P30104

FOR FURTHER ACTION See paragraphs 1 and 4 below

International application No.
PCT/GB92/01082

International filing date
 (day/month/year)

17/06/92

Applicant

SMITHKLINE BEECHAM PLC et al.

1. The applicant is hereby notified that the international search report has been established and is transmitted herewith.

Filing of amendments and statement under Article 19:

The applicant is entitled, if he so wishes, to amend the claims of the international application (see Rule 46):

When? The time limit for filing such amendments is normally 2 months from the date of transmittal of the international search report; however, for more details, see the notes on the accompanying sheet.

Where? To the International Bureau of WIPO
 34, chemin des Colombettes
 1211 Geneva 20, Switzerland
 Facsimile No.: (41-22) 740.14.35

For more detailed instructions, see the notes on the accompanying sheet.

2. The applicant is hereby notified that no international search report will be established and that the declaration under Article 17(2)(a) to that effect is transmitted herewith.

3. With regard to the protest against payment of (an) additional fee(s) under Rule 40.2; the applicant is notified that:

the protest together with the decision thereon has been transmitted to the International Bureau together with the applicant's request to forward the texts of both the protest and the decision thereon to the designated Offices.

no decision has been made yet on the protest; the applicant will be notified as soon as a decision is made.

4. **Further action(s):** The applicant is reminded of the following:

Shortly after 18 months from the priority date, the international application will be published by the International Bureau. If the applicant wishes to avoid or postpone publication, a notice of withdrawal of the international application, or of the priority claim, must reach the International Bureau as provided in Rules 90bis.1 and 90bis.3, respectively, before the completion of the technical preparations for international publication.

Within 19 months from the priority date, a demand for international preliminary examination must be filed if the applicant wishes to postpone the entry into the national phase until 30 months from the priority date (in some Offices even later).

Within 20 months from the priority date, the applicant must perform the prescribed acts for entry into the national phase before all designated Offices which have not been elected within 19 months from the priority date or could not be elected because they are not bound by Chapter II.

Name and mailing address of the International Searching Authority
 European Patent Office, P.B. 5818 Patentlaan 2
 NL-2280 HV Rijswijk
 Tel. (+ 31-70) 340-2040, Tx. 31 651 epo nl,
 Fax: (+ 31-70) 340-3016

Authorized officer

Dagmar Frank
 Mme Dagmar FRANK

NOTES TO FORM PCT/ISA/220

These notes are intended to give the basic instructions concerning the filing of amendments under article 19. The Notes are based on the requirements of the Patent Cooperation Treaty and of the Regulations and the Administrative Instructions under that Treaty. In case of discrepancy between these Notes and those requirements, the latter are applicable. For more detailed information, see also the PCT Applicant's Guide, a publication of WIPO.

In these notes, "Article", "Rule", and "Section" refer to the provisions of the PCT, the PCT Regulations and the PCT administrative Instructions respectively.

INSTRUCTIONS CONCERNING AMENDMENTS UNDER ARTICLE 19

The applicant has, after having received the international search report, one opportunity to amend the claims of the international application. It should however be emphasized that, since all parts of the international application (claims, description and drawings) may be amended during the international preliminary examination procedure, there is usually no need to file amendments of the claims under Article 19 except where, e.g. the applicant wants the latter to be published for the purposes of provisional protection or has another reason for amending the claims before international publication. Furthermore, it should be emphasized that provisional protection is available in some States only.

What parts of the international application may be amended?

The claims only.

The description and the drawings may only be amended during international preliminary examination under Chapter II.

When?

Within 2 months from the date of transmittal of the international search report or 16 months from the priority date, whichever time limit expires later. It should be noted, however, that the amendments will be considered as having been received on time if they are received by the International Bureau after the expiration of the applicable time limit but before the completion of the technical preparations for international publication (Rule 46.1).

Where not to file the amendments?

The amendments may only be filed with the International Bureau and not with the receiving Office or the International Searching Authority (Rule 46.2).

Where a demand for international preliminary examination has been/is filed, see below.

How?

Either by cancelling one or more entire claims, by adding one or more new claims or by amending the text of one or more of the claims as filed.

A replacement sheet must be submitted for each sheet of the claims which, on account of an amendment or amendments, differs from the sheet originally filed.

All the claims appearing on a replacement sheet must be numbered in Arabic numerals. Where a claim is cancelled, no renumbering of the other claims is required. In all cases where claims are renumbered, they must be renumbered consecutively (Administrative Instructions, Section 205(b)).

What documents must/may accompany the amendments?

Letter (Section 205(b)):

The amendments must be submitted with a letter.

The letter will not be published with the international application and the amended claims. It should not be confounded with the "Statement under Article 19(1)" (see below, under "Statement under Article 19(1)").

The letter must indicate the differences between the claims as filed and the claims as amended. It must, in particular, indicate, in connection with each claim appearing in the international application (it being understood that identical indications concerning several claims may be grouped), whether

- (i) the claim is unchanged;
- (ii) the claim is cancelled;
- (iii) the claim is new;
- (iv) the claim replaces one or more claims as filed;
- (v) the claim is the result of the division of a claim as filed.

NOTES TO FORM PCT/ISA/220 (continued)

The following examples illustrate the manner in which amendments must be explained in the accompanying letter:

1. [Where originally there were 48 claims and after amendment of some claims there are 51]: "Claims 1 to 29, 31, 32, 34, 35, 37 to 48 replaced by amended claims bearing the same numbers; Claims 30, 33 and 36 unchanged; new claims 49 to 51 added."
2. [Where originally there were 15 claims and after amendment of all claims there are 11]: "Claims 1 to 15 replaced by amended claims 1 to 11."
3. [Where originally there were 14 claims and the amendments consist in cancelling some claims and in adding new claims]: "Claims 1 to 6 and 14 unchanged; claims 7 to 13 cancelled; new claims 15, 16 and 17 added." or "Claims 7 to 13 cancelled; new claims 15, 16 and 17 added; all other claims unchanged."
4. [Where various kinds of amendments are made]: "Claims 1-10 unchanged; claims 11 TO 13, 18 and 19 cancelled; claims 14, 15 and 16 replaced by amended claim 14; claim 17 subdivided into amended claims 15, 16 and 17; new claims 20 and 21 added."

"Statement under article 19(1)" (Rule 46.4)

The amendments may be accompanied by a statement explaining the amendments and indicating any impact that such amendments might have on the description and the drawings which cannot be amended under Article 19(1).

The statement will be published with the international application and the amended claims.

The statement should be brief, it should not exceed 500 words if in English or if translated into English.

It should not be confounded with and does not replace the letter indicating the differences between the claims as filed and as amended. It must be filed on a separate sheet and must be identified as such by a heading, preferably by using the words "Statement under Article 19(1)."

It should not contain any disparaging comments on the international search report or the relevance of citations contained in that report. Reference to citations, relevant to a given claim, contained in the international search report may be made only in connection with an amendment of that claim.

In what language?

The amendments must be made in the language in which the international application is published. The letter and any statement accompanying the amendments must be in the same language as the international application if that language is English or French; otherwise, it must be in English or French, at the choice of the applicant.

Consequence if a demand for international preliminary examination has already been filed?

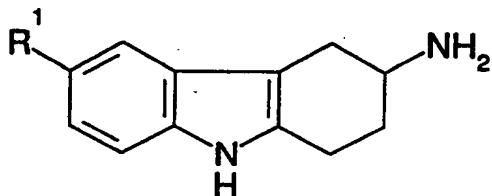
If, at the time of filing any amendments under Article 19, a demand for international preliminary examination has already been submitted, the applicant must preferably, at the same time of filing the amendments with the International Bureau, also file a copy of such amendments with the International Preliminary Examining Authority (see Rule 62.2(a), first sentence).

Consequence with regard to translation of the international application for entry into the national phase?

The applicant's attention is drawn to the fact that, where upon entry into the national phase, a translation of the claims as amended under Article 19 may have to be furnished to the designated/elected Offices, instead of, or in addition to, the translation of the claims as filed.

For further details on the requirements of each designated/elected Office, see Volume II of the PCT Applicant's Guide.

It is believed that compounds of formula (I) wherein R² and R³ both represent hydrogen are novel. Thus in a further aspect the present invention provides compounds of formula (IA) :



5

Formula (IA)

wherein R¹ is as hereinbefore defined, and salts thereof.

10

The present invention further provides the following specific compounds which are also believed to be novel :

15 3-Amino-6-cyano-1,2,3,4-tetrahydrocarbazole hydrochloride,
 (+)-3-amino-6-carboxamido-1,2,3,4-tetrahydrocarbazole hydrochloride,
 (-)-3-amino-6-carboxamido-1,2,3,4-tetrahydrocarbazole hydrochloride,

20 3-amino-6-methoxy-1,2,3,4-tetrahydrocarbazole hydrochloride,
 3-amino-6-bromo-1,2,3,4-tetrahydrocarbazole hydrochloride,
 3-amino-6-methyl-1,2,3,4-tetrahydrocarbazole oxalate,
 3-amino-6-ethoxycarbonyl-1,2,3,4-tetrahydrocarbazole oxalate,
 3-amino-6-(N-methyl carboxamido)-1,2,3,4-tetrahydrocarbazole hemioxalate,

25 3-amino-6-cyanomethyl-1,2,3,4-tetrahydrocarbazole oxalate,
 3-amino-6-(N-methylsulphonamidomethyl)-1,2,3,4-tetrahydrocarbazole oxalate,

30 3-amino-6-chloro-1,2,3,4-tetrahydrocarbazole oxalate,
 3-amino-6-trifluoromethyl-1,2,3,4-tetrahydrocarbazole oxalate,
 3-amino-6-n-butyloxy-1,2,3,4-tetrahydrocarbazole oxalate,
 3-amino-6-sulphonamido-1,2,3,4-tetrahydrocarbazole oxalate,

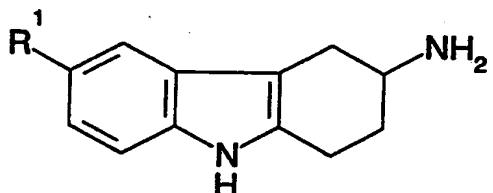
Replaced by MRT 34

$-(CH_2)_nCN$, $-(CH_2)_nCONR^5R^6$, $-(CH_2)_nSO_2RN^5R^6$ or
 C₁-6alkanoylamino, and R⁵ and R⁶ are as hereinbefore defined.

4. Use of a compound according to claim 3 wherein R¹
 5 is a group $-(CH_2)_nCONR^5R^6$, wherein n is zero and R⁵ and R⁶
 each independently represent hydrogen, methyl or ethyl.

5. Use of a compound according to any of claims 1 to
 3 wherein R² and R³ each independently represent hydrogen,
 10 methyl or ethyl.

6. A compound of formula (IA) :



15

Formula (IA)

wherein R¹ is as hereinbefore defined, or a salt thereof.

20 7. A compound of formula (I) selected from :

3-Amino-6-cyano-1,2,3,4-tetrahydrocarbazole;

(+)-3-amino-6-carboxamido-1,2,3,4-tetrahydrocarbazole;

(-)-3-amino-6-carboxamido-1,2,3,4-tetrahydrocarbazole;

25 3-amino-6-methoxy-1,2,3,4-tetrahydrocarbazole;

3-amino-6-bromo-1,2,3,4-tetrahydrocarbazole;

3-amino-6-methyl-1,2,3,4-tetrahydrocarbazole;

3-amino-6-ethoxycarbonyl-1,2,3,4-tetrahydrocarbazole;

3-amino-6-(N-methyl carboxamido)-1,2,3,4-tetrahydrocarbazole;

30 3-amino-6-cyanomethyl-1,2,3,4-tetrahydrocarbazole;

3-amino-6-(N-methylsulphonamidomethyl)-1,2,3,4-tetrahydro-
 carbazole;

3-amino-6-chloro-1,2,3,4-tetrahydrocarbazole;

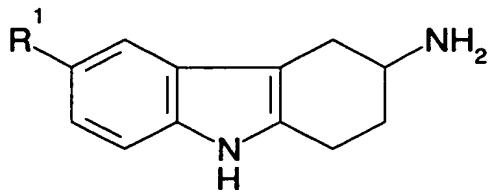
3-amino-6-trifluoromethyl-1,2,3,4-tetrahydrocarbazole;
3-amino-6-n-butyloxy-1,2,3,4-tetrahydrocarbazole;
3-amino-6-sulphonamido-1,2,3,4-tetrahydrocarbazole;
3-amino-6-nitro-1,2,3,4-tetrahydrocarbazole;
5 3-amino-6-(N,N-dimethylcarboxamido)-1,2,3,4-tetrahydrocarbazole;
3-amino-6-(piperidin-1-ylcarbonyl)-1,2,3,4-tetrahydrocarbazole;
3-amino-6-(pyrrolidin-1-ylcarbonyl)-1,2,3,4-tetrahydrocarbazole;
10 3-amino-6-(N,N-diethylcarboxamido)-1,2,3,4-tetrahydrocarbazole;
3-Amino-6-(acetamido)-1,2,3,4-tetrahydrocarbazole;
3-amino-6-methanesulphonamido-1,2,3,4-tetrahydrocarbazole;
15 3-amino-6-carboxamidomethyl-1,2,3,4-tetrahydrocarbazole;
3-methylamino-6-carboxamido-1,2,3,4-tetrahydrocarbazole;
3-ethylamino-6-carboxamido-1,2,3,4-tetrahydrocarbazole;
3-n-propylamino-6-carboxamido-1,2,3,4-tetrahydrocarbazole;
3-i-propylamino-6-carboxamido-1,2,3,4-tetrahydrocarbazole;
20 3-dimethylamino-6-carboxamido-1,2,3,4-tetrahydrocarbazole;
3-benzylamino-6-carboxamido-1,2,3,4-tetrahydrocarbazole;
3-pyrrolidinyl-6-carboxamido-1,2,3,4-tetrahydrocarbazole;
3-(N-(methyl)ethylamino)-6-carboxamido-1,2,3,4-tetrahydrocarbazole; and
25 3-amino-6-(2-carboxamidoethyl)-1,2,3,4-tetrahydrocarbazole;
or a salt thereof.

8. A method of treatment of a condition wherein a 5-HT₁-like agonist is indicated, which comprises administering
30 to a subject in need thereof an effective amount of a compound of formula (I) as hereinbefore defined or a physiologically acceptable salt thereof.

9. A process for the preparation of a novel compound
35 of formula (I), which comprises :

A) Reaction of a compound of formula (II) :

10. A pharmaceutical composition comprising a compound of formula (I) or a physiologically acceptable salt thereof and a physiologically acceptable carrier.



5

Formula (IA)

wherein R¹ is as hereinbefore defined with the proviso that R¹ is not hydrogen, hydroxy, methoxy or benzyloxy, and salts thereof.

10

The present invention further provides the following specific compounds which are also believed to be novel :

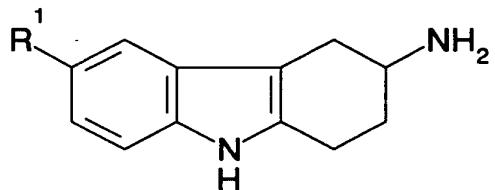
- 3-Amino-6-cyano-1,2,3,4-tetrahydrocarbazole hydrochloride,
- 15 (+)-3-amino-6-carboxamido-1,2,3,4-tetrahydrocarbazole hydrochloride,
- (-)-3-amino-6-carboxamido-1,2,3,4-tetrahydrocarbazole hydrochloride,
- 3-amino-6-bromo-1,2,3,4-tetrahydrocarbazole hydrochloride,
- 20 3-amino-6-methyl-1,2,3,4-tetrahydrocarbazole oxalate,
- 3-amino-6-ethoxycarbonyl-1,2,3,4-tetrahydrocarbazole oxalate,
- 3-amino-6-(N-methyl carboxamido)-1,2,3,4-tetrahydrocarbazole hemioxalate,
- 3-amino-6-cyanomethyl-1,2,3,4-tetrahydrocarbazole oxalate,
- 25 3-amino-6-(N-methylsulphonamidomethyl)-1,2,3,4-tetrahydrocarbazole oxalate,
- 3-amino-6-chloro-1,2,3,4-tetrahydrocarbazole oxalate,
- 3-amino-6-trifluoromethyl-1,2,3,4-tetrahydrocarbazole oxalate,
- 30 3-amino-6-n-butyloxy-1,2,3,4-tetrahydrocarbazole oxalate,
- 3-amino-6-sulphonamido-1,2,3,4-tetrahydrocarbazole oxalate,
- 3-amino-6-nitro-1,2,3,4-tetrahydrocarbazole oxalate,
- 3-amino-6-(N,N-dimethylcarboxamido)-1,2,3,4-tetrahydrocarbazole hemioxalate,

$-(CH_2)_nCN$, $-(CH_2)_nCONR^5R^6$, $-(CH_2)_nSO_2RN^5R^6$ or C_{1-6} alkanoylamino, and R^5 and R^6 are as hereinbefore defined.

4. Use of a compound according to claim 3 wherein R^1 5 is a group $-(CH_2)_nCONR^5R^6$, wherein n is zero and R^5 and R^6 each independently represent hydrogen, methyl or ethyl.

5. Use of a compound according to any of claims 1 to 3 wherein R^2 and R^3 each independently represent hydrogen, 10 methyl or ethyl.

6. A compound of formula (IA) :



15

Formula (IA)

wherein R^1 is as hereinbefore defined with the proviso that R^1 is not hydrogen, hydroxy, methoxy or benzyloxy, or a salt 20 thereof.

7. A compound of formula (I) selected from :

- 3-Amino-6-cyano-1,2,3,4-tetrahydrocarbazole;
- 25 (+)-3-amino-6-carboxamido-1,2,3,4-tetrahydrocarbazole;
- (-)-3-amino-6-carboxamido-1,2,3,4-tetrahydrocarbazole;
- 3-amino-6-bromo-1,2,3,4-tetrahydrocarbazole;
- 3-amino-6-methyl-1,2,3,4-tetrahydrocarbazole;
- 3-amino-6-ethoxycarbonyl-1,2,3,4-tetrahydrocarbazole;
- 30 3-amino-6-(N-methyl carboxamido)-1,2,3,4-tetrahydrocarbazole;
- 3-amino-6-cyanomethyl-1,2,3,4-tetrahydrocarbazole;
- 3-amino-6-(N-methylsulphonamidomethyl)-1,2,3,4-tetrahydro-
- carbazole;
- 3-amino-6-chloro-1,2,3,4-tetrahydrocarbazole;
- 35 3-amino-6-trifluoromethyl-1,2,3,4-tetrahydrocarbazole;

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3-amino-6-n-butyloxy-1,2,3,4-tetrahydrocarbazole;
3-amino-6-sulphonamido-1,2,3,4-tetrahydrocarbazole;
3-amino-6-nitro-1,2,3,4-tetrahydrocarbazole;
3-amino-6-(N,N-dimethylcarboxamido)-1,2,3,4-tetrahydro-
5 carbazole;
3-amino-6-(piperidin-1-ylcarbonyl)-1,2,3,4-tetrahydro-
carbazole;
3-amino-6-(pyrrolidin-1-ylcarbonyl)-1,2,3,4-tetrahydro-
carbazole;
10 3-amino-6-(N,N-diethylcarboxamido)-1,2,3,4-tetrahydro-
carbazole;
3-Amino-6-(acetamido)-1,2,3,4-tetrahydrocarbazole;
3-amino-6-methanesulphonamido-1,2,3,4-tetrahydrocarbazole;
3-amino-6-carboxamidomethyl-1,2,3,4-tetrahydrocarbazole;
15 3-methylamino-6-carboxamido-1,2,3,4-tetrahydrocarbazole;
3-ethylamino-6-carboxamido-1,2,3,4-tetrahydrocarbazole;
3-n-propylamino-6-carboxamido-1,2,3,4-tetrahydrocarbazole;
3-i-propylamino-6-carboxamido-1,2,3,4-tetrahydrocarbazole;
3-dimethylamino-6-carboxamido-1,2,3,4-tetrahydrocarbazole;
20 3-benzylamino-6-carboxamido-1,2,3,4-tetrahydrocarbazole;
3-pyrrolidinyl-6-carboxamido-1,2,3,4-tetrahydrocarbazole;
3-(N-(methyl)ethylamino)-6-carboxamido-1,2,3,4-tetrahydro-
carbazole; and
3-amino-6-(2-carboxamidoethyl)-1,2,3,4-tetrahydrocarbazole;
25 or a salt thereof.

8. A method of treatment of a condition wherein a
5-HT₁-like agonist is indicated, which comprises administering
to a subject in need thereof an effective amount of a compound
30 of formula (I) as hereinbefore defined or a physiologically
acceptable salt thereof.

9. A process for the preparation of a compound of
formula (I) as defined in claim 6 or claim 7 which comprises :

35

A) Reaction of a compound of formula (II) :

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10. A pharmaceutical composition comprising a compound of formula (I) as defined in claim 6 or claim 7 or a physiologically acceptable salt thereof and a physiologically acceptable carrier.

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PATENT COOPERATION TREATY

PCT

INTERNATIONAL SEARCH REPORT

(PCT Article 18 and Rules 43 and 44)

Applicant's or agent's file reference JF/JMcD/P30104	FOR FURTHER ACTION see Notification of Transmittal of International Search Report (Form PCT/ISA/220) as well as, where applicable, item 5 below.	
International application No. PCT/ GB92/ 01082	International filing date (<i>day/month/year</i>) 17/06/92	(Earliest) Priority Date (<i>day/month/year</i>) 26/06/91
Applicant SMITHKLINE BEECHAM PLC et al.		

This international search report has been prepared by this International Searching Authority and is transmitted to the applicant according to Article 18. A copy is being transmitted to the International Bureau.

This international search report consists of a total of 4 sheets.
 It is also accompanied by a copy of each prior art document cited in this report.

1. Certain claims were found unsearchable (see Box I).
2. Unity of invention is lacking (see Box II).
3. The international application contains disclosure of a nucleotide and/or amino acid sequence listing and the international search was carried out on the basis of the sequence listing
 - filed with the international application.
 - furnished by the applicant separately from the international application,
 - but not accompanied by a statement to the effect that it did not include matter going beyond the disclosure in the international application as filed.
 - Transcribed by this Authority
4. With regard to the title, the text is approved as submitted by the applicant.
 the text has been established by this Authority to read as follows:

USE OF TETRAHYDROCARBAZONE DERIVATIVES AS 5HT1 RECEPTOR AGONISTS

5. With regard to the abstract,
 - the text is approved as submitted by the applicant.
 - the text has been established, according to Rule 38.2(b), by this Authority as it appears in Box III. The applicant may, within one month from the date of mailing of this international search report, submit comments to this Authority.
6. The figure of the drawings to be published with the abstract is:

Figure No. _____	<input type="checkbox"/> as suggested by the applicant.	<input checked="" type="checkbox"/> None of the figures.
	<input type="checkbox"/> because the applicant failed to suggest a figure.	
	<input type="checkbox"/> because this figure better characterizes the invention.	

INTERNATIONAL SEARCH REPORT

International application No.

PCT/GB92/01082

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This international search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. Claims Nos.:

because they relate to subject matter not required to be searched by this Authority, namely:

ALTHOUGH CLAIM 8 IS DIRECTED TOWARDS A METHOD OF TREATMENT OF THE HUMAN/ANIMAL TODAY THE SEARCH HAS BEEN CARRIED OUT AND BASED UPON THE ALLEGED EFFECTS OF THE COMPOUND.

2. Claims Nos.:

because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:

3. Claims Nos.:

because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.

2. As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.

3. As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:

4. No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

The additional search fees were accompanied by the applicant's protest.

No protest accompanied the payment of additional search fees.